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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/813,718	03/21/2001	Paul Schimmel	TSRI 817.0	3346

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EXAMINER	
NICKOL, GARY B	
ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 11/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/813,718	SCHIMMEL ET AL.	
	Examin r	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this c mmunication app ars on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *9-35 and 38-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,36 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Election filed August 13, 2002 (Paper No. 7) in response to the Office Action of July 2, 2002 is acknowledged and has been entered.

Claims 1-48 are pending in the application.

Claims 9-35, and 38-48 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 1-8, 36-37 are currently under prosecution.

Applicant's election with traverse of Group I, claims 1-8, 36-37 in Paper No 7 is acknowledged. The traversal is on the ground(s) that Group V should be examined together with the elected Group I since the claims of group V are also drawn to isolated peptides and compositions thereof. Applicants argue that there is no indication that Groups I and V are independent since the subject matter in Group V is also directed to truncated tryptophanyl- tRNA synthetase polypeptides. This is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups (including Groups I and V) are distinct for the reasons set forth in Paper No. 7. Furthermore, the peptides of Group I differ from the peptides of Group V in that they include distinct functional (i.e. angiogenic versus chemokine activities) and structural differences (i.e. differences in nucleotide domains) from those claimed in Group V. This would involve different searches and the consideration of independent issues. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search,

particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. Applicants further argue that the Office Action failed to show or provide adequate reasoning to support the restriction requirement while further arguing that the requirement for restriction is not mandatory. This argument has been considered but is not found persuasive. The reasoning for the restriction requirement was set forth in Paper No. 7 (see pages 4-5). Furthermore, although the restriction requirement may not be mandatory for all cases, the requirement for restriction must be considered on a case-by-case basis.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Specification

The specification is objected to (i.e., pages 23 and 24) for recitation of SEQ ID:9 in reference to the polypeptides of the invention since SEQ ID NO:9 is a polynucleotide. Corrections are required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 6 recite the limitation the "truncated tRNA" synthetase polypeptide in Claim 1. There is insufficient antecedent basis for this limitation from which these claims

depend. This rejection can be obviated by amending the claims to recite the truncated "tryptophanyl-tRNA" synthetase polypeptide.

Claims 1, 6, and 36 are further rejected as vague and indefinite for reciting "and fragments thereof comprising the amino acid sequence –Asp-Leu-Thr-" in Claim 6 as it is not clear how this limitation further defines the independent claim. For example, claim 1 is drawn to an isolated polypeptide comprising a truncated tryptophanyl-tRNA synthetase polypeptide comprising a Rossmann fold nucleotide binding domain, wherein the isolated polypeptide is capable of regulating vascular endothelial cell function. How does "fragments thereof comprising the amino acid sequence –Asp-Leu-Thr-" further define the isolated polypeptide? Are these fragments independent of the Rossmann fold nucleotide binding domain? Are they appendages? Essentially, the metes and bounds of the claim cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an isolated polypeptide comprising a truncated tryptophanyl-tRNA synthetase polypeptide comprising a Rossmann fold nucleotide binding domain, wherein

the isolated polypeptide is capable of regulating vascular endothelial cell function (Claim 1); wherein the polypeptide is angiogenic (Claim 4).

The specification clearly limits "angiogenic" polypeptides to those comprising a truncated TyrRS or "tyrosyl-tRNA synthetase" (specification, page 56, Example 6) while clearly limiting truncated tryptophanyl-tRNA synthetases to "angiostatic" activity (page 57, Example 7). Furthermore, the specification refers to truncated TyrRS (i.e. mini TyrRS) as angiogenic and truncated TrpRS as angiostatic (page 60, line 26). Thus, the specification does not contain a written description of the claimed invention, that is: a truncated tryptophanyl-tRNA synthetase polypeptide that is angiogenic.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Also, one cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

Claims 1, 6, and 37 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a truncated tryptophanyl-tRNA synthetase polypeptide comprising a Rossmann fold nucleotide binding domain, wherein the isolated polypeptide is capable of regulating vascular endothelial cell function wherein the truncated tRNA synthetase

polypeptide is a member of the group consisting of: a polypeptide consisting essentially of amino acid residues 48-471 of SEQ ID NO:10, a polypeptide consisting essentially of amino acid residues 71-471 of SEQ ID NO:10, a polypeptide of approximately 47 kD molecular weight produced by cleavage of the polypeptide of SEQ ID NO:10 with polymorphonuclear leucocyte elastase and compositions thereof with a pharmaceutically suitable excipient, does not reasonably provide enablement for a truncated tryptophanyl-tRNA synthetase polypeptide comprising a Rossmann fold nucleotide binding domain, wherein the isolated polypeptide is capable of regulating vascular endothelial cell function wherein the truncated tRNA synthetase polypeptide is a member of the group consisting of fragments thereof comprising the amino acid sequence **-Asp-Leu-Thr-** and a composition thereof with a pharmaceutically suitable excipient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to isolated polypeptides comprising a truncated tryptophanyl-tRNA synthetase polypeptide comprising a Rossmann fold nucleotide binding domain, wherein the isolated polypeptide is capable of regulating vascular endothelial cell

function (Claim 1); wherein the truncated tRNA synthetase polypeptide is a member of the group consisting of:

-a polypeptide consisting essentially of amino acid residues 48-471 of SEQ ID NO:10.

-a polypeptide consisting essentially of amino acid residues 71-471 of SEQ ID NO:10.

-a polypeptide of approximately 47 kD molecular weight produced by cleavage of the polypeptide of SEQ ID NO:10 with polymorphonuclear leucocyte elastase.

-fragments thereof comprising the amino acid sequence **-Asp-Leu-Thr-** (Claim 6); and compositions thereof and a pharmaceutically suitable excipient (Claim 36).

This includes a whole universe of peptides comprising a Rossmann fold nucleotide binding domain including "fragments thereof" comprising the tripeptide, **-Asp-Leu-Thr** and compositions thereof with a pharmaceutically suitable excipient. Further, because of the indefinite nature of the claim language, it is assumed for examination purposes that fragments thereof include any amino acid fragment thereof (i.e., any fragment derived from the truncated tryptophanyl-tRNA synthetase polypeptide) which further includes the amino acid sequence **Asp-Leu-Thr-** as previously described above in the rejections of claims 1,6, and 37 under USC 112 2nd paragraph.

The specification teaches (page 9) that "truncated tRNA synthetase polypeptides" mean polypeptides that are shorter than the corresponding full length tRNA synthetase". The specification further teaches (page 22) that fragments (when referring to polypeptides) are polypeptides which retain substantially the same biological function or activity as such polypeptides. This includes (page 24, line 25) conservative and non-conservative substitutions or replacements with a substituent group or fusions. The specification further teaches (page 57, line

19+) that the presence in mammalian TrpRS molecules of a Rossmann nucleotide binding fold and DLT sequence (Asp-Leu-Thr-), in place of the ELR motif, suggests that mammalian TrpRS molecules may function as angiostatic factors.

However, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to whole universe of peptides comprising a Rossmann fold nucleotide binding domain including "fragments thereof" comprising the tripeptide, -**Asp-Leu-Thr** and compositions thereof with a pharmaceutically suitable excipient, and applicant has not enabled all of these types of modified proteins because it has not been shown that these modified proteins are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and fusions thereof of the disclosed polypeptide can be tolerated that will allow the protein to function as claimed, including deletions, truncations, substitutions and fusions of the Rossmann fold domain. While

it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all peptides comprising a truncated tryptophanyl-tRNA synthetase polypeptide comprising a Rossmann fold nucleotide binding domain including "fragments thereof" comprising the tripeptide, -**Asp-Leu-Thr** and compositions thereof with a pharmaceutically suitable excipient. Therefore, in view of the lack of predictability of the prior art and the breadth of the claims, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4-8, and 36-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Fleckner *et al.* (Proc.Natl.Acad.Sci. Vol. 88, pages 11520-11524, 1991).

The claims are drawn to an isolated polypeptide comprising a truncated tryptophanyl-tRNA synthetase polypeptide comprising a Rossmann fold nucleotide binding domain, wherein the isolated polypeptide is capable of regulating vascular endothelial cell function (Claim 1); wherein the truncated polypeptide has a size of at least about 46 kilodaltons (Claim 2); wherein the polypeptide is angiogenic (Claim 4); or angiostatic (Claim 5); wherein the truncated tRNA synthetase polypeptide is a member of the group consisting of:

-a polypeptide consisting essentially of amino acid residues 48-471 of SEQ ID NO:10.

-a polypeptide consisting essentially of amino acid residues 71-471 of SEQ ID NO:10.

-a polypeptide of approximately 47 kD molecular weight produced by cleavage of the polypeptide of SEQ ID NO:10 with polymorphonuclear leucocyte elastase.

-fragments thereof comprising the amino acid sequence Asp-Leu-Thr- (Claim 6); wherein the polypeptide is mammalian (Claim 7); wherein the polypeptide is human (Claim 8); and compositions comprising the isolated polypeptides of claim 1 or claim 6 and a pharmaceutically suitable excipient (Claims 36 and 37).

Fleckner *et al.* teach an isolated human polypeptide comprising a truncated tryptophanyl-tRNA synthetase polypeptide which is at least about 46 kilodaltons (abstract and Figure 5) wherein the truncated tryptophanyl-tRNA synthetase polypeptide comprises fragments thereof comprising the Asp-Leu-Thr fragment (see attached sequence listing). Fleckner *et al.* further teach said truncated tryptophanyl-tRNA synthetase polypeptide as compositions in pharmaceutically suitable excipients (i.e., buffers) (see page 11521, 1st column, 4th paragraph). Although Fleckner *et al.* do not specifically teach that the truncated tryptophanyl-tRNA

synthetase polypeptide comprises a "Rossmann fold nucleotide binding domain" the claimed product appears to be the same as the prior art polypeptide since Fleckner *et al.* further teach that the truncated tryptophanyl-tRNA synthetase polypeptide retained biological activity (abstract, page11523, 2nd column, 2nd paragraph). Thus, absent evidence to the contrary, the prior art polypeptide inherently comprises a Rossmann fold nucleotide binding domain. Furthermore, although the reference does not specifically teach that the truncated polypeptide is capable of regulating vascular endothelial cell function, or that the truncated polypeptide is angiogenic or angiostatic, the claims are drawn to the product *per se* and inherently, such a polypeptide is capable of regulating vascular endothelial cell function and is angiogenic or angiostatic. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claims 1-5, 7, 36 are further rejected under 35 U.S.C. 102(b) as being anticipated by Lemaire *et al.* (Eur.J.Biochem. Vol. 51. No. 1, pages 237-52, 1975).

The claims are drawn to an isolated polypeptide comprising a truncated tryptophanyl-tRNA synthetase polypeptide comprising a Rossmann fold nucleotide binding domain, wherein the isolated polypeptide is capable of regulating vascular endothelial cell function (Claim 1);

wherein the truncated polypeptide has a size of at least about 46 kilodaltons (Claim 2); wherein the truncated tRNA synthetase polypeptide has amino-terminal truncation (Claim 3); wherein the polypeptide is angiogenic (Claim 4); or angiostatic (Claim 5); wherein the polypeptide is mammalian (Claim 7); and compositions comprising the isolated polypeptides of claim 1 and a pharmaceutically suitable excipient (Claim 36).

Lemaire *et al.* teach an isolated mammalian polypeptide comprising a truncated tryptophanyl-tRNA synthetase polypeptide (TRS_{82}) which has a size of at least about 46 kilodaltons wherein the truncated tRNA synthetase polypeptide has amino-terminal truncation (see abstract, page 244, and page 245, 2nd column). Lemaire *et al.* further teach a composition comprising a truncated tryptophanyl-tRNA synthetase polypeptide and a pharmaceutically acceptable carrier (i.e, buffers) (see Figure 8, page 247). Although Lemaire *et al.* do not specifically teach that the truncated tryptophanyl-tRNA synthetase polypeptide comprises a "Rossmann fold nucleotide binding domain" the claimed product appears to be the same as the prior art polypeptide as Lemaire *et al.* further teach that the truncated tryptophanyl-tRNA synthetase polypeptide retained biological activity (page 247). Thus, absent evidence to the contrary, the prior art polypeptide inherently comprises a Rossmann fold nucleotide binding domain. Furthermore, although the reference does not specifically teach that the truncated polypeptide is capable of regulating vascular endothelial cell function, or that the truncated polypeptide is angiogenic or angiostatic, the claims are drawn to the product *per se* and inherently, such a polypeptide is capable of regulating vascular endothelial cell function and is angiogenic or angiostatic. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the

same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
October 30, 2002